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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/624,218	07/22/2003	Nikolay Korokhov	D6463	1033

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EXAMINER	
PRIEBE, SCOTT DAVID	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 08/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/624,218	KOROKHOV ET AL.	
	Examiner	Art Unit	
	Scott D. Priebe, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1,5-7 and 11-13* is/are allowed.

6)☒ Claim(s) *3,9 and 14-16* is/are rejected.

7)☒ Claim(s) *2,4,8 and 10* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 July 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *20040917*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

5.0.0

DETAILED ACTION

Specification

The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: Claim 14 recites the terms "operably linked" and "dendritic cell-specific promoter". The term "operably linked" is not used in the specification. The term "dendritic cell-specific promoter" is not used in the specification (nor is the term "promoter").

Claim Objections

Claims 2-4 and 8-10 are objected to because of the following informalities:

Claims 2 and 8 improperly recite a Markush group; "SEQ ID No. 1-4" should be --SEQ ID NOs: 1, 2, 3, and 4--. Claims 3, 4, 9, and 10 each recite "the carboxy terminal." The term "terminal" is an adjective not a noun, and should be replaced with --terminus--.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim14 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described

in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 14 is directed to an adenovirus vector of claim 7 wherein the recited genes are operably linked to a "dendritic cell-specific promoter." Claim 14 is the sole description of such a promoter, i.e. there is no antecedent basis for the claim terminology in the original specification (see objection to the specification). The specification does not identify any examples of a dendritic cell-specific promoter. The specification does not provide either a complete or partial structure of such a promoter or disclose any distinguishing characteristics of such a promoter.

The court and the Board have repeatedly held (*Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*,18 USPQ2d 1016 (CA FC, 1991); *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993); *Fiddes v. Baird*, 30 USPQ2d 1481 (BPAI 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)) that an adequate written description of a nucleic acid requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it, irrespective of the complexity or simplicity of the method; what is required is a description of the nucleic acid itself. It is not sufficient to define DNA solely by its principal biological property, because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any DNA with that biological property. Naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. When one is unable to envision the detailed constitution of a complex chemical compound having a particular function, such as a nucleic acid, so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, i.e., until after the nucleic acid has been

isolated. Thus, claiming all DNA's that achieve a result without defining what means will do so is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. This is the case here, where the specification does not contain even a single example of the recited promoter or describe a method for isolating one. Thus, there is no evidence that Applicant was in possession of even a species of promoter readable on claim 14, much less a genus of such promoters, or of an adenovirus that contains one.

Claims 15 and 16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for embodiments where the CD40+ cells are *in vitro* or in culture, does not reasonably provide enablement for embodiments where the cells are *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 15 and 16 are directed to a method for the transfer of a gene encoding a heterologous protein into a CD40+ cell, e.g. a dendritic cell, by treating the cell with an adenovirus vector containing the gene and having a ligand that binds CD40 on the surface of the cell. The claims broadly embrace any cell, either *in vivo* or *in vitro*. The specification does not enable the practice of the method for delivering the heterologous gene to a CD40+ cell *in vivo*.

The specification does not explicitly teach a specific use for transfecting CD40+ cells *in vivo* with an adenovirus vector. The specification describes prior art on the use of dendritic cells (DCs), which are one type of CD40+ cells, for *ex vivo* immunotherapy for cancer, where the DCs are transfected with an adenovirus vector encoding a tumor associated antigen, and then administered to an animal model for cancer or to a cancer patient with the goal of inducing an

immune response against tumor cells that express the antigen (page 7), i.e. using adenovirus vector transfected DCs as a cancer vaccine. The specification discusses prior art pertaining to the low efficiency of transfecting DCs *ex vivo* with adenovirus vectors, and points out that this low efficiency impairs efficient production of transfected DCs *ex vivo* and would be a serious impediment to direct *in vivo* immunization with the adenovirus (page 9-10). The specification then describes adenovirus vectors having their tropism altered by modification with proteins comprising a ligand that would bind CD40 on a DC, and that such alterations significantly improved the efficiency of the adenovirus for transfecting DCs (page 11), and indicates that the present invention aims to provide similarly targeted adenovirus that are easier to produce (pages 12-13). Consequently, the specification implies that the adenovirus vectors may be used *in vivo* for anti-cancer immunization targeting DCs or *ex vivo* for producing DCs to be used as anti-cancer vaccines. No other use for practicing the claimed method on CD40+ cells *in vivo* is described either explicitly or implicitly.

Bodey et al. (Anticancer Res 2000;20:2665-76) reviews cancer vaccines in cancer immunotherapy, and teaches:

> The cancer vaccine approach to therapy is based on the notion that the immune system could possibly mount a rejection strength response against the neoplastically transformed cell conglomerate. However, due to the low immunogenicity of tumor associated antigens, downregulation of MHC molecules, the lack of adequate costimulatory molecule expression, secretion of immune inhibitory cytokines, etc., such expectation are rarely fulfilled. ... faulty antigen presentation which could result in tolerance induction to the antigens contained within the vaccine, and subsequent rapid tumor progression.

and

> The theoretical basis for all of these approaches is very well founded. Animal models, albeit highly artificial, have yielded promising results. Clinical trials in humans, however, have been somewhat disappointing...

(emphasis added, page 2665, Abstract). Bodey teaches that the failure of tumor vaccines is due to the selective pressure exerted by the immune response directed at tumor antigens that are carried by some tumor cells, which ends up selecting for tumor cell clones lacking the antigen that are highly resistant, poorly immunogenic, and extremely aggressive (para. bridging page 2673-2674).

Radoja et al. (Mol Med 6: 465-479, 2000) teaches that cancer-induced defective cytotoxic T lymphocyte is probably another mechanism how tumor antigen escape immune surveillance.

> The notion that a deficit in immune cell functions permits tumor growth has received experimental support with the discovery of several different biochemical defects in T lymphocytes that infiltrate cancers.

(abstract).

> Accumulation of circulating antitumor immunoglobulin G in cancer patients show that the priming phase of antitumor immune response is functional during the relatively slow process of nascent tumor growth. ... In both human cancer patients and rodents bearing tumors of different histologic origin, systemic immunity is not profoundly suppressed ... However, inhibition of a specific antitumor immune response has been observed frequently. A variety of mechanism have been proposed to account for defective antitumor immune response, including: secretion of suppressive factors in the tumor microenvironment, the lack of expression of costimulatory signals on tumor cells, induction of regulatory T cells having a suppressive phenotype, loss of antigen presentation function in the tumor, loss of expression of HLA class I antigen presenting molecules in tumors, tumor-induced T-cell signaling defects, loss of tumor antigen expression, immunological ignorance and, since many tumor antigens are either unmodified self or epitopes closely related to self, the reduction of the repertoire of potential high affinity antitumor T-cell clones during T-cell maturation in the thymus.

(Introduction, pages 465-466). As taught by Bodey and Radoja, the success or failure of cancer immunotherapy is determined by many distinct factors both from the nature of the antigen itself and the host immune responses. The etiology and the mechanism leading to a given cancer differ significantly among different cancer types. Failure far exceeds success in view of tumor

immunotherapy as a whole, and Bodey suggests that the use of cancer vaccines may be in vain (page 2674). Both show that the area of anti-cancer vaccination was unpredictable.

Basak et al. (Viral Immunol. 17 (2): 2182-196, June 2004) reviews the state of the art of using adenovirus vectors for cancer vaccines from before the instant application was filed and after. Basak notes that while adenovirus vectors have performed well in preclinical models, their application to patients is limited due to host immune responses and consequent toxicity. Basak notes that a variety of strategies have been developed to address the limitations, but that these "have not been systematically combined and/or tested for their application to vaccine development." (page 183). Basak (page 183-185) summarizes the known immune responses to the administration of adenovirus vectors, innate response, virus-specific antibody response, and virus-specific cellular immunity, all of which negatively impact the efficiency of transfection and the efficiency of subsequent gene expression from the vector. One of the main problems is that most human patients have been previously exposed to adenoviruses, and adenovirus vector is rapidly cleared and destroyed in these instances. After reviewing these immune responses, Basak states: "[T]hese immune responses may confound the use of FG-AdV vectors in anti-cancer vaccines." The various strategies suggested to overcome the limitations imposed by the immune system are summarized on pages 185-189, only two of which is described in the instant specification-modifying the vector to enhance transfection of DCs (page 188) and *ex vivo* transfection of DCs. Basak teaches that the *ex vivo* approach using adenovirus infected DCs avoids most of the problems associated with *in vivo* administration of the adenovirus vector. Even so, early phase clinical trials with *ex vivo* transfected DCs show that only a minority of patients respond to the treatment (pages 188-189). Consequently, one would expect that *in vivo*

administration of an adenovirus vector would be substantially less effective than *ex vivo* therapy with transfected DCs. The disclosure of Basak shows that the use of adenovirus vector for *in vivo* anti-cancer immunization had not yet been developed, and thus unpredictable.

The specification does not provide any specific guidance as to how the adenovirus vector should be used *in vivo* to transfect CD40+ cells generally or DCs specifically. It does not teach routes of administration, dosage or administration schedule, or any ancillary treatments that may be required. The specification provides no working examples for transfection of DCs either *in vitro* or *in vivo*, much less a working example that shows effective immunization against cancer in either an animal model for cancer, e.g. a mouse having a tumor implant, or in an animal or human with cancer. While the conditions for transfection of CD40+ cells can be controlled, and CD40+ cells can be transfected with even untargeted adenoviral vectors, transfection of CD40+ cells *in vivo* cannot be controlled. An adenovirus vector administered *in vivo* encounters harsher conditions than one administered to cultured cells. The targeting of the vector in the claimed invention involves a non-covalent association of the targeting ligand and the modified adenoviral fiber. The specification provides no evidence that this association is stable *in vitro*, much less that it would be stable *in vivo*. If it is not stable *in vivo*, then at best the vector would be as inefficient in transfecting a DC as an untargeted vector. At worst, it would be less efficient, as might be expected for embodiments where a substantial region of the fiber is replaced with the T4 fibritin protein.

Therefore, in view of the breadth of the claims relative to the teachings presented in the specification, the relatively undeveloped state of the prior art regarding anti-cancer vaccines in general and the undeveloped state of the art for targeting DCs by *in vivo* administration

specifically, the unpredictability of anti-cancer vaccination in general and of *in vivo* adenovirus vector anti-cancer immunization specifically, the paucity of guidance for carrying out the invention, and the lack of relevant working examples, undue experimentation would be required in order to practice embodiments of the invention involving *in vivo* transfection of CD40+ cells for a practical purpose.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3 and 9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 3 and 9 recite the limitation "the HI loop" in line 2 of each. There is insufficient antecedent basis for this limitation in the claim. The corresponding independent claims do not specify that the fiber has an HI loop, nor is the presence of an HI loop in the fiber inherent, e.g. see claim 4.

Allowable Subject Matter

Claims 1-17 are free of the prior art. The closest prior art is represented by US 6,284,742, which discloses adenoviral vectors having a normal fiber protein with a targeting ligand non-covalently attached to the fiber, but where the targeting ligand is one antigen binding region of a bispecific antibody wherein the second antigen binding region binds the knob of the adenoviral

fiber. There is no prior art of record that suggests using zipper peptide pairs as a means of attaching targeting ligands to a modified fiber of an adenoviral vector.

Claims 3 and 9 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, 2nd paragraph, set forth in this Office action.

Claims 2, 4, 8 and 10 would be allowable if rewritten to overcome the objections set forth in this Office action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott D. Priebe, Ph.D. whose telephone number is (571) 272-0733. The examiner can normally be reached on M-F, 8:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Scott D. Priebe

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Art Unit 1633